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ORIGINAL ARTICLE

Frequency of Medication Use among Liver Transplant Candidates and Recipients during the COVID-19 Pandemic

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Abstract

Introduction: The liver is recognized as a primary target in COVID-19 due to its susceptibility to viral infection and its prominent role in the body's immune and metabolic responses. The present study aims to investigate the frequency of supplement and medication use among liver transplant recipients and candidates during the COVID-19 pandemic.

Methods: This cross-sectional study included demographic and clinical information from 170 liver transplant recipients and candidates who had sought care at the Guilan Transplant Center in Rasht, Iran. The participants' history of taking supplements, antibiotics, immunosuppressants, antiviral and gastrointestinal medications, and their COVID-19 infection history were recorded. Statistical analysis of the data was performed using SPSS software (version 22).

Results: Of the total 170 individuals in the study, 84(49.4%) were candidates for liver transplants, while 86(51.6%) had already received liver transplants. Among liver transplant candidates, 2(2.4%) were infected with COVID-19, and one died; among the liver transplant recipients, 8(9.3%) patients had COVID-19, and three died. Among liver transplant recipients, the most frequently consumed supplements, immunosuppressive, antibiotics, antiviral, and gastrointestinal medications were Vitamin D (77.9%), Prednisolone (90.1%), Cotrimoxazole (5.8%), Tenofovir (16.8%), and Pantoprazole (74.4%), respectively. Among liver transplants, the candidates were folic acid (32.1%), Prednisolone (20.2%), Azithromycin (1.2%), Tenofovir (5.9%), and Pantoprazole (51.2%).

Conclusion: Individuals who have received liver transplants and have a history of medication use are more susceptible to contracting COVID-19. The findings underscored the vulnerability of transplant recipients, particularly those on long-term immunosuppressive therapy, to SARS-CoV-2 infection. The prevalence of underlying diseases in both groups further emphasized the need for heightened vigilance and tailored preventive measures.

Key words: Antibiotics, COVID-19, Immunosuppressive Agents, Liver Transplantation

Introduction

The COVID-19 pandemic was caused by the virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). With close to 30,000 RNA letters, SARS-CoV-2 can infiltrate cells and commandeer them to replicate new viruses. There are still drawbacks to our understanding of COVID-19 disease that remain unclear (1–3). The clinical symptoms of COVID-19 disease vary from mild to severe that can result in hospitalization in the intensive care unit (ICU)

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and even death, especially in patients with underlying diseases, such as autoimmune diseases, cardiovascular diseases, chronic kidney diseases, chronic liver disease, pulmonary diseases, etc. (4–7).

In addition to the results of polymerase chain reaction (PCR) test and computed tomography (CT) scan, a high level of C reactive protein (CRP) is considered as a general inflammatory factor in the COVID-19 disease. Impaired immunity caused by the disease, characterized by lymphopenia, is considered a basic feature in diagnosis (7). Therefore, in patients with COVID-19, various immunosuppressive, antibiotics, antiviral, gastrointestinal medications are prescribed due to the severity of the condition and symptoms. Among these patients, candidates for organ transplantation or organ transplant recipients face an elevated risk of sickness and death due to the co-existence of organ dysfunctions and receiving wide-spectrum medications (8,9).

Considering the proven role of the angiotensin-converting enzyme *2 (*ACE2) enzyme in the pathogenesis of COVID-19 and the abundant production of this enzyme in the liver and biliary epithelial cells, the liver is considered a target organ for this virus. The increase of liver markers such as alanine transferase (ALT) and aspartate aminotransferase (AST) can be related to the direct cytopathic effect of the virus itself or the damage caused by the immune system following virus stimulation. On the other hand, prescribed medications for COVID-19, such as Statins, Remdesivir, and Tocilizumab, can be hepatotoxic. For individuals experiencing end-stage chronic liver disease or acute liver failure, liver transplantation is the ultimate treatment option (10,11).

Considering that the Guilan province, Iran, is among the important and great units of liver transplantation in Iran and has covered many patients, special attention is paid to these patients due to the widespread COVID-19, and the pattern of medications and supplements is essential. In this regard, we aimed to investigate the frequency of some medications and supplements among liver transplant candidates and recipients according to the severity of COVID-19 infection.

Methods

A group of 170 patients participated in this cross-sectional study, selected from 300 liver transplant candidates and recipients registered at the Guilan Transplant Center, University of Medical Sciences, Rasht, Iran, from 2021 to 2022. The demographic data and clinical characteristics of the patients were recorded from the patients' archives. The data included age, gender, underlying disease, and a history of receiving supplements, antibiotics, immunosuppressive, antiviral, and gastrointestinal medication. Positive results of PCR test and CT scan for SARS-CoV-2 infection confirmed the COVID-19 infection. The patients with incomplete data were excluded from the study.

The study sample size was determined using Cochran's formula for sample size calculation. The data were reported by Mean ± Standard division (SD), numbers, and percentages. The statistical analysis of all data was performed using SPSS software (version 22). This study design was approved by the Ethical Committee of Guilan University of Medical Sciences (IR.GUMS.REC.1400.423).

Results

Based on the obtained results, out of 170 patients, 49.4% were liver transplant candidates and 51.6% were liver transplant recipients. This study showed that a low frequency of COVID-19 infection in all patients with liver dysfunction. Among liver transplant candidates, 2(2.4%) of them had COVID-19 disease, and one died. Among the liver transplant recipients, 8(9.3%) were infected with SARS-CoV-2, and three died. The mean age of liver transplant recipients was 50.24 ± 12.83 years old (18-73 years old), 59(68.6%) were men, and the mean age of the liver transplant candidates was 42.97 ± 16.56 years old (1-72 years old) and 48(57.1%) of them were men. Among the liver transplant recipients, about 59(68.6%) had a history of underlying diseases, and in a group of liver transplant candidates, about 63(75.0%) of the patients had underlying diseases.

The most regular immunosuppressive medications among liver transplant recipients were Prednisolone (90.1%), Prograf (88.4%), Myfortic (43%), and Selcept (48.8%), respectively. Prednisolone (20.2%) was the most frequent immunosuppressive medication among liver transplant candidates. The most common antibiotics among liver transplant recipients were Cotrimoxazole (5.8%) and Tavanex (4.7%), and among liver transplant candidates were Azithromycin (1.2%). The most frequent antiviral medication among liver transplant candidates and recipients was Tenofovir, 5.9% and 18.6%, respectively. Among liver transplant recipients and candidates, the most frequent gastrointestinal medications were Pantoprazole and Ursodeoxycholic acid (74.4% and 62.8%) and (51.2% and 47.6), respectively. Folic acid, calcium, and Vitamin D were the joint supplements among liver transplant recipients and candidates (62.8%,

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77.9%, and 18.6%) and (32.1%, 27.4%, and 17.9%), respectively (Table 1).

Table 1: Frequency of received medications among liver transplant candidates and recipients in the Guilan Transplant Unit, Rasht, Iran

Medications		Liver transplant recipients (n=84) n (%)	Liver transplant candidates (n=86) n (%)	COVID-19 infections n (%)	
				Liver transplant recipients (n=8)	Liver transplant candidates (n=2)
Immuno-suppressive	Prednisolone	78 (90.1)	17 (20.2)	5 (62.5)	-
	Prograf	75 (88.4)	2 (2.4)	4 (50.0)	-
	Myfortic	37 (43.0)	1 (1.2)	5 (62.5)	-
	Celsept	42 (48.8)	1 (1.2)	3 (37.5)	-
	Everolimus	5 (5.8)	-	-	-
	Sirolimus	10 (11.6)	-	3 (37.5)	-
	Azathioprine	-	16 (19.0)	-	-
Anti-biotics	Azithromycin	1 (1.2)	1 (1.2)	1 (12.5)	-
	Tavanex	4 (4.7)	-	3 (37.5)	-
	Co-trimoxazole	5 (5.8)	-	1 (12.5)	-
Anti-viral	Tenofovir	16 (18.6)	5 (5.9)	2 (25.0)	1 (50.0)
	Hydroxychloroquine	3 (3.5)	-	2 (25.0)	-
	Valganciclovir	2 (2.3)	-	1 (12.5)	-
Gastrointestinal	Pantoprazole	64 (74.4)	43 (51.2)	5 (62.5)	1 (50.0)
	Omeprazole	7 (8.1)	6 (7.1)	1 (12.5)	-
	Ursodeoxycholic acid	54 (62.8)	40 (24.6)	3 (37.5)	-
	Mesalazine	17 (19.8)	8 (9.5)	1 (12.5)	-
	Famotidine	2 (2.3)	-	-	-
	Dimethicone	-	-	-	-
	Ranitidine	-	2 (2.4)	-	-
	GeriLact	1 (1.2)	1 (1.2)	-	-
	Livegol	-	5 (6.0)	-	-
	Lactulose	-	16 (19.0)	-	-
Supplements	Folic acid	53 (62.8)	27 (32.1)	5 (62.5)	-
	Calcium D	67 (77.9)	23 (27.4)	5 (62.5)	-
	Vitamin B1	-	4 (4.8)	-	-
	Vitamin B6	1 (1.2)	1 (1.2)	-	-
	Vitamin B complex	-	3 (3.6)	-	-
	Vitamin C	-	1 (1.2)	-	-
	Vitamin D	16 (18.6)	15 (17.9)	-	-
	Vitamin E	-	5 (6.0)	-	-
	Multivitamin	4 (4.7)	18 (61.4)	1 (12.5)	-
	Zinc	-	7 (8.3)	-	-
	Magnesium	2 (2.4)	1 (1.2)	1 (12.2)	-
	Hematinic	-	2 (2.4)	-	-

Discussion

Individuals who undergo organ transplant surgery require immunosuppressive medication to prevent rejection, putting them at increased risk of various infections. Following liver transplantation and because of the use of immunosuppressive medication, it is crucial to avoid unnecessary additional medication for optimal long-term survival. Immunocompromised patients, including liver transplant recipients and candidates, require specific infection control measures to prevent the acquisition of COVID-19 infection. In the current study, most of the patients were middle-aged, with the majority of men, and only 10 patients out of 170 liver transplant candidates and recipients were infected with SARS-CoV-2 infection. The commonly reported immunosuppressive, antibiotics, antiviral, and gastrointestinal medication among both groups were Prednisolone, Cotrimoxazole/Azithromycin, Tenofovir, and Pantoprazole. Additionally, folic acid and calcium D were the most frequent supplements that the patients consumed.

Studies reported that supplements, including vitamin C, D, zinc, and omega-3 have increased during the COVID-19 pandemic (12,13). In a study, it has been illustrated that patients with COVID-19 experienced different degrees of liver abnormalities. They suggested treatment with Acetaminophen and avoidance of non-steroidal

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anti-inflammatory medications in cirrhosis. However, using antiviral medications in patients with liver complications and drug interactions after liver transplantation should be considered (14). A cohort study on medication-related problems in liver transplant recipients demonstrated that 98 medication-related problems were identified in 53 patients. The most frequent medication-related problems were: adverse drug reactions (22.4%), nonadherence (19.3%), unnecessary drugs (16.3%), and undertreatment (12.2%) (15).

However, it is difficult to distinguish whether the increase in liver markers is due to the infection of COVID-19 or the use of hepatotoxic drugs, the flare-up of the disease in patients with liver dysfunction who use immunosuppressive medications, or acute cellular rejection in liver transplant recipients should not be considered only under the impact of COVID-19 infection (16,17). Along with the recommended antiviral medications for COVID-19, some antibiotics for concomitant bacterial infections are prescribed for hospitalized patients with COVID-19 (18,19). On the other hand, the consumption of supplements has increased during the outbreak of COVID-19 to enhance the function of the immune system (20–22). In this regard, by considering that liver dysfunction is multifactorial and whether the liver damage is related to underlying liver disease or due to the use of prescribed medication for the treatment of COVID-19, it is vital to consider the pattern of medication in patients with end-stage liver diseases during co-infection of viral or microbial factors.

The study's limitations included its cross-sectional nature and single-center design, which restrict the generalizability of the findings and the ability to establish causal relationships. Further investigations are necessary for the generalizability of these results to different populations. Moreover, some confounders might derive significant inferences from the results, including underlying diseases, genetics profiles, and other viral infections. Therefore, further studies are needed to improve the clinical management of liver transplant candidates and recipients.

Conclusions

The present study highlighted the relatively low incidence of COVID-19 infection among patients with liver dysfunction, with liver transplant recipients exhibiting a higher infection rate and mortality compared to liver transplant candidates. The findings underscored the vulnerability of transplant recipients, particularly those on long-term immunosuppressive therapy, to SARS-CoV-2 infection. The prevalence of underlying diseases in both groups further emphasized the need for heightened vigilance and tailored preventive measures.

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Conflict of Interest

The authors declare that they have no competing interests.

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